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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/986,174	11/07/2001	Nabil Hanna	P 0280732 2000-30-0261VUS	4956

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/986,174	HANNA, NABIL	
	Examiner	Art Unit	
	MISOOK YU, Ph.D	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16, 17, 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.80

DETAILED ACTION

Election/Restrictions

This application contains claims 1-15, and 18-22 drawn to an invention nonelected with traverse in the Paper filed on 08/30/2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-15, and 18-22 remain withdrawn for reason of record from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-27 are pending. Claims 16, 17, and 23-27 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office action contains new grounds of rejection.

Priority

Applicant's amendment to the first line of the specification filed on 05/10/05 has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: the amendment does not include the relationship (i.e., continuation, divisional, or continuation-in-part) to PCT/US01/40835. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. Note (37 CFR 1.78(a)(2) and (a)(5).

Claim Objections, Withdrawn

The objection of claims 16, and 17 are withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103, Maintained

Claims 16, and 17 remain rejected, and the **new claims 23-27 are newly rejected** under 35 U.S.C. 103(a) as being unpatentable over Demidem et al., Cancer Biother Radiopharm., June 1997, vol. 12, pages 177-186 in view of Hagenbeek et al., J Clin Oncol., January 1998, vol. 16 pages 41-47, further in view of Reff et al., 1994, Blood, vol. 83, pages 435-445.

Claims 16, 17, and 23-27 are drawn to method of enhancing apoptosis of lymphoma B cells using an immunoconjugate comprising an anti-CD20 antibody or a fragment thereof fused at its carboxy terminus to IFN-alpha-2a.

Applicant summaries what Demidem teaches, and then argues that "nowhere in the teachings of Demidem is there a discussion or suggestion of using an anti-CD20/IFN-alpha-2a fusion protein as a single vehicle for targeting cell mediated cytotoxicity of B-cell lymphoma cells via the subject's own natural killer cells and/0r macrophages." Applicant also argues that the claimed invention uses a fusion protein, which allows for specific targeting of tumor cells to attract and potentiate cell-mediated cytotoxicity either by antibody-dependent cell-mediated cytotoxicity, phagocytic or direct killing. This cell-mediated cytoxicity only occurs because the subject's own natural killer cells, polymorphonuclear cells, lymphocyte-activated killer cells, macrophages, and monocytes recognize interferon alpha-2a portion of the novel fusion protein. In Demidem only teaches using medicinal cytotoxic agents to kill B-cell lymphoma cells

that have had their resistance pathways altered by pre-treatment with a mouse anti-CD20 antibody. In addition, Demidem uses two steps (administering anti-CD20 antibody first followed by administering cytotoxic agents), while the claimed invention uses one step of administering a fusion protein comprising anti-CD fused to interferon alpha-2a, thus one of ordinary skill in the art studying the disclosure of Demidem would not be taught or even suggested to practice the claimed invention. With regard to Hagenbeek (secondary reference), and Reff (tertiary reference), applicant argues that these two references do little to overcome the failings of Demidem, and in fact teach away from the claimed invention. Hagenbeek does not teach a method wherein an immunoconjugate fusion protein pinpoints B-cell lymphoma cells and enhances apoptosis via interferon. Hagenbeek simply teaches interferon can be used as a maintenance treatment measure to prolong the time of re-progression of B cell lymphoma cells after chemotherapy. Hagenbeek does not teach or suggest targeting tumor cells expressing CD20, and in fact concludes its study by stating the overall survival rate was not influenced by interferon treatments, thus one of ordinary skill would not have been motivated to use interferon as a means to cause apoptosis in B-cell lymphoma by fusing inferferon-alpha-2a to an antiCD20 antibody over Demidem in view of Hagenbeek. As for the tertiary reference (Reff), applicant argues that Reff does little to overcome the failings of the primary and the secondary references. Applicant argues that none of the cited references teach the claimed invention of one step method of using the anti-CD20 antibody to interferon alpha-2a fusion protein to directly target B cell lymphoma cells using the subject's own cell-mediated cytotoxic cells.

These arguments have been fully considered but found unpersuasive for the following reasons. As stated in the previous Office action, Demidem et al., teach that an anti-CD20 antibody, more specifically Rituximab (IDEC C2B, note paragraph 0006 of the instant specification as compared to the title of Demidem et al) as recited in the new claim 25, enhances apoptosis of B lymphoma cells (note the title, and abstract), mediate "ADCC" (note page 178, left column, 2nd full paragraph) as recited in the new claim 24, and also teach that pretreatment with the anti-CD20 antibody enhances cell killing of the target cells by other cytotoxic drugs.

Demidem et al., do not teach interferon alpha 2a as one of the other cytotoxic drugs. However, Hagenbeek et al., teach how to make and purify the human recombinant interferon alfa-2a had been known well before the effective filing date of the instant application. Hagenbeek et al., further teach that the human recombinant interferon alfa-2a has a good effect for patients with B cell lymphoma i.e. stages III and IV low-grade malignant non-Hodgkin's lymphoma (note the abstract). In addition, Reff et al., 1994, Blood, vol. 83, pages 435-445 teach that the state of art of making a fusion protein of an anti-CD20 antibody or a fragment thereof fused at its carboxy terminus to IFN-alpha-2a. Reff et al., at Figs. 1 and 3 teach that how to construct a expression vector encoding anti-CD20 antibody, and also teach many useful restriction sites that could be used to fuse the human recombinant interferon alfa-2a. Therefore it would have been obvious to one of the ordinary skill in the art to make and use an anti-CD20 antibody or a fragment thereof that is fused at its carboxy terminus to IFN-alpha-2a in the method of enhancing apoptosis in B cell lymphoma, thereby treating the lymphoma

with a reasonable expectation of success since Hagenbeek et al., teach how to make recombinant interferon alfa-2a, and Reff et al., teach how to construct anti-CD20 antibody expression construct. One of an ordinary skill would have been motivated to make the fusion to minimize the painful injections by giving one fusion protein instead of two separate injections, and/or purifying one protein instead of two proteins, thus reducing cost and saving time.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In response to applicant's argument that, the fact that applicant has recognized another advantage (i.e. targeting of tumor cells to attract and potentiate cell-mediated cytotoxicity either by antibody-dependent cell-mediated cytotoxicity, phagocytic or direct killing) which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claims 16, and 17 remain rejected, and **new claims 23-27 are newly rejected** under **35 U.S.C. 103(a)** as being unpatentable over Davis et al., July 2000, Clinical Cancer Research, vol. 6, pages 2644-2652 in view of Taji et al., Jpn. J. Cancer Res., July 1998, vol. 89, pages 748-756.

Claims 16, 17, and 23-27 are drawn to method of enhancing apoptosis of lymphoma B cells using an immunoconjugate comprising an anti-CD20 antibody or a fragment thereof fused at its carboxy terminus to IFN-alpha-2a.

Applicant argues that Davis fails to teach or suggest the instantly claimed invention, which unexpectedly provides an improved immunoconjugate that not only enhances antibody-dependent cellular cytotoxicity and phagocytic activities, but also lowers the toxicity and increases the serum half-life. The fusion protein, as opposed to the separate administration of IFN and anti-CD20 antibody as in the case of Davis, simultaneously targets B-cell lymphoma cells as well as uses the subject's effector cells to kill the targeted B-cell lymphoma cells. The anti-CD20 antibody of Davis is not fused to IFN-alpha-2a, therefore would not specifically target IFN-alpha-2a, to a tumor cell. Fusing anti-CD 20 antibody to IFN-alpha-2a is not suggested or taught in Davis. As for Taji, applicant argues that the reference does not teach enhancing apoptosis of B-cell lymphoma by using anti-CD20 antibody fused to IFN-alpha-2a. Rather Taji teaches mechanism of action of anti-CD20 antibody for causing apoptosis of B-cell lymphoma

cells. Neither Davis nor Taji teach or suggest the claimed invention of using the applicant's immunoconjugate. One in the art would not reasonably expect improved success of the IFN/anti-CD20 antibody fusion protein based upon Davis in view of Taji.

These arguments have been fully considered but found unpersuasive for the following reasons: First, applicant's argument that the instantly claimed method specifically target IFN-alpha-2a, to a tumor cell is considered as arguing limitation not present in the claims because the instant claims 16 and 23 as currently construed say that IFN-alpha-2a is targeted to IFN-alpha-2a receptor expressed on the surface of an effector cell, wherein the effector cell is NK, LAK, PMN, or monocyte cell. In other words, IFN-alpha-2a is specifically targeted to a NK, LAK, PMN, or monocyte cell that expresses the receptor that IFN-alpha-2a binds to. In addition, the only manipulative step that could be enforced by the patent law is the method step of administering a product for a given population of "a subject". Once the product (a therapeutically effective entity) is administered to a subject, how the therapeutically effective entity does its job inside the body of the subject (i.e. the mechanism of action of the product) is outside the patent law protection. Here, recruiting NK, LAK, PMN, or monocyte cells by IFN-alpha-2a is a mechanism of action, not a manipulative step. As stated in the previous Office action, Davis teaches at page 2645, right column that an anti-CD20 antibody (i.e., Rituximab) and IFN had synergistic effect on preclinical trials, therefore the authors of the study set out to do the human clinical trials, and found that the combination therapy between anti-CD20 antibody, and interferon alpha 2a had a good result in humans as well. With respect to the argument that the anti-CD20 antibody of

Davis is not fused to IFN-alpha-2a, this rejection is not 102 anticipation rejection, but rejection under 35 U.S.C.103(a) because the product being used are not identical.

In response to applicant's argument that there is no suggestion or teaching of the claimed fusion protein in Davis, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As stated in the previous Office action, Davis teaches that anti-CD 20 antibody and IFN-alpha-2a has synergistic effect.

Davis, et al., do not teach whether the good result is from enhancing apoptosis of the B lymphoma cells.

However, Taji et al., teach that an anti-CD20 antibody enhances apoptosis of B lymphoma cells (note the title and also Fig. 4 at page 752).

Therefore it would have been obvious to one of the ordinary skill in the art to make and use an anti-CD20 antibody or a fragment thereof is fused at its carboxy terminus to IFN-alpha-2a in the method of enhancing apoptosis in B cell lymphoma, thereby treating the lymphoma with a reasonable expectation of success since how to make recombinant interferon alfa-2a, and how to construct anti-CD20 antibody expression construct had been well known in the art before the effective filing date of the instant application. One of an ordinary skill would have been motivated to make the

fusion to minimize the painful injections by giving one fusion protein instead of two separate injections, and/or purifying one protein instead of two proteins, thus reducing cost and saving time.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the engineered antibody fragment whose sequence has been published, does not reasonably provide enablement for the specifically recited antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 25 recites specific monoclonal antibodies produced by specific cell lines.

It is apparent that the recited antibodies of "IF5, Ibritumomab, 1H4, and anti-B1" are required to practice the claimed invention, because they are specifically required in the claims. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement

requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the cell lines listed in claim 25. See 37 CFR 1.802.

Although the specification at paragraphs [0006] discloses that some of the CDR sequences of the monoclonal antibodies of the instant claim 25 have been published, the specification does not provide a repeatable method for obtaining the cell lines producing the specifically recited monoclonal antibodies, and they do not appear to be readily available material. Deposit of the cell lines would satisfy the enablement requirements of 35 U.S.C. 112.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the

biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Conclusion

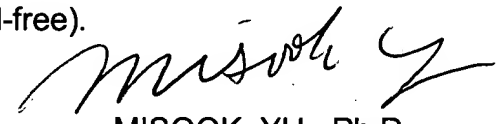
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Art Unit 1642